Cellular Development as a Hybrid Control System

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Motivating Example: Pattern Formation in *Xenopus*

- Reference:
  - Collier, Monk, Maini, Lewis
  - Marnellos, Mjolsness
- Cell biology
  - *Xenopus* embryo epidermal cell differentiation
    - Initially homogeneous population
    - Emergence of ciliated cell
  - Mechanism of cell fate decision
    - Delta-Notch signaling pathway
    - Delta and Notch: transmembrane proteins
      - Delta promotes ciliation
      - Notch inhibits ciliation

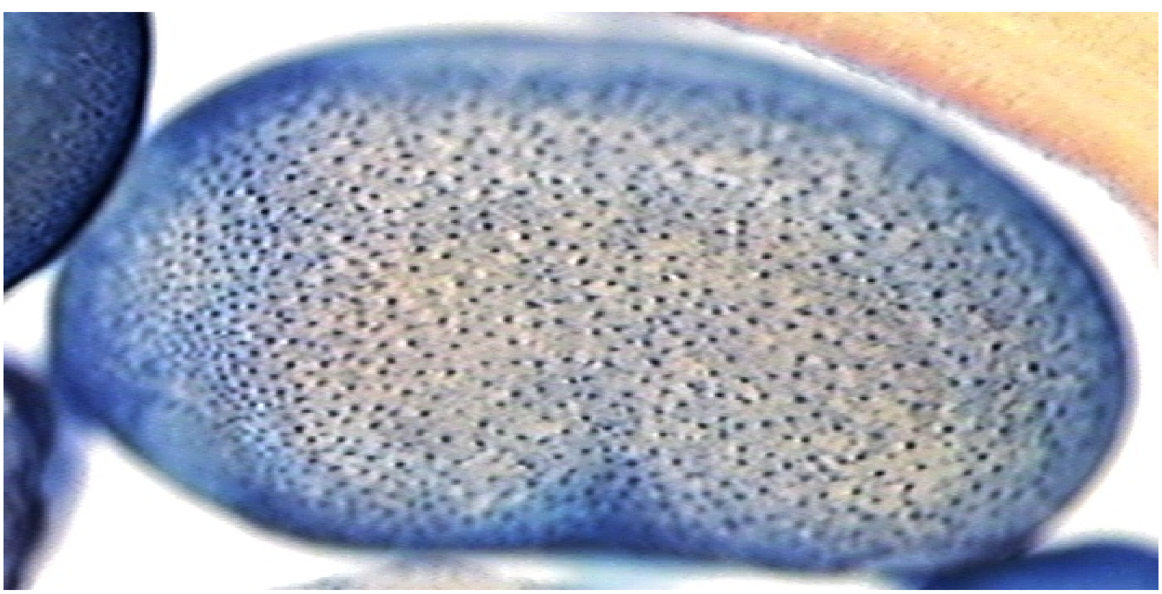

Figure 1: *Xenopus* embryo labeled by α-*tubulin*, a marker for ciliated cell precursors

Model Properties

- Assumptions:
  - Intercellular Delta-Notch signaling occurs only through direct contact
  - Notch production: triggered only by high Delta concentrations in neighboring cells
  - Delta production: triggered only by low Notch concentration in same cell
  - Both proteins decay at constant rates
- Planar cell array

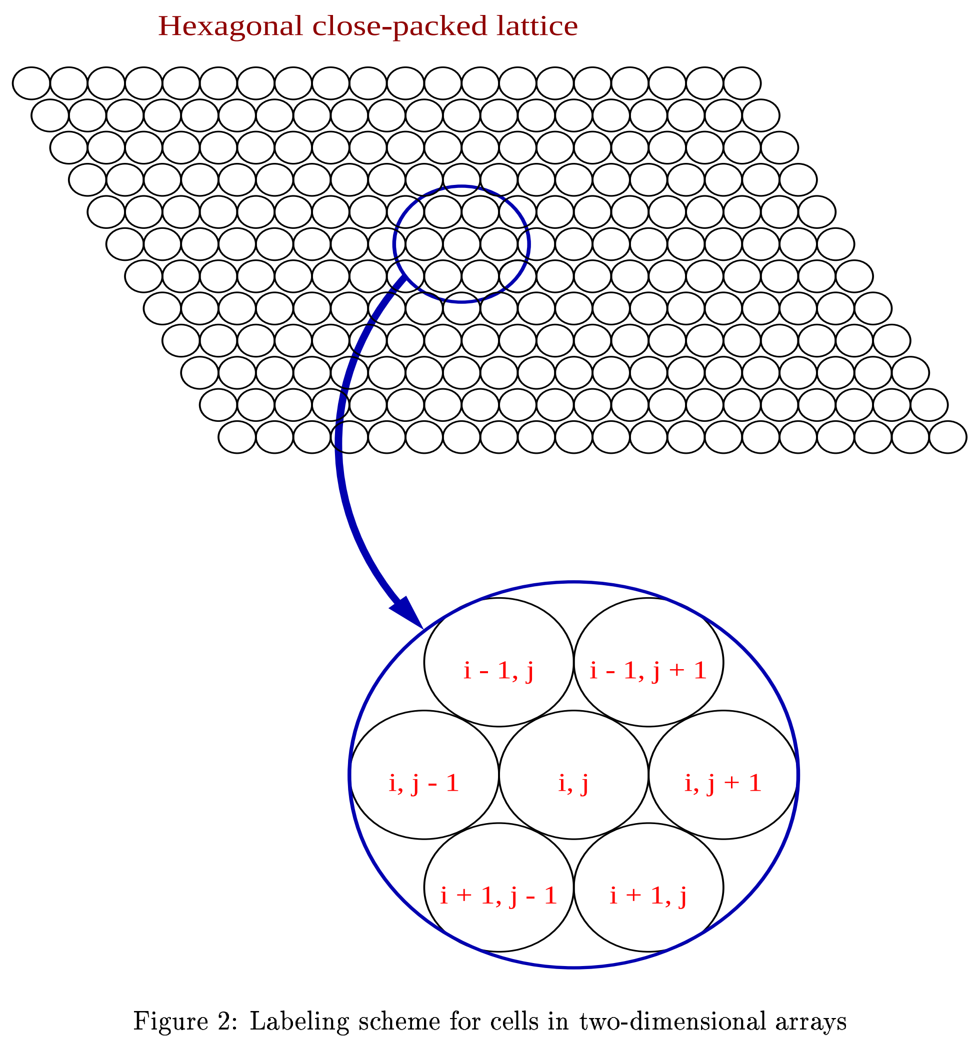

Figure 2: Labeling scheme for cells in two-dimensional arrays

Hybrid System Model

- Each cell: 4-mode hybrid automaton
  - 2 state variables

    v_D: Delta concentration

    v_N: Notch concentration
  - Inputs

    $u_D = -v_N$

    $u_N = \Sigma_{i=1}^{6} v_D^i$
  - Transition relations

    $u_D \geq h_D$: Delta production is on, otherwise off

    $u_N \geq h_N$: Notch production is on, otherwise off

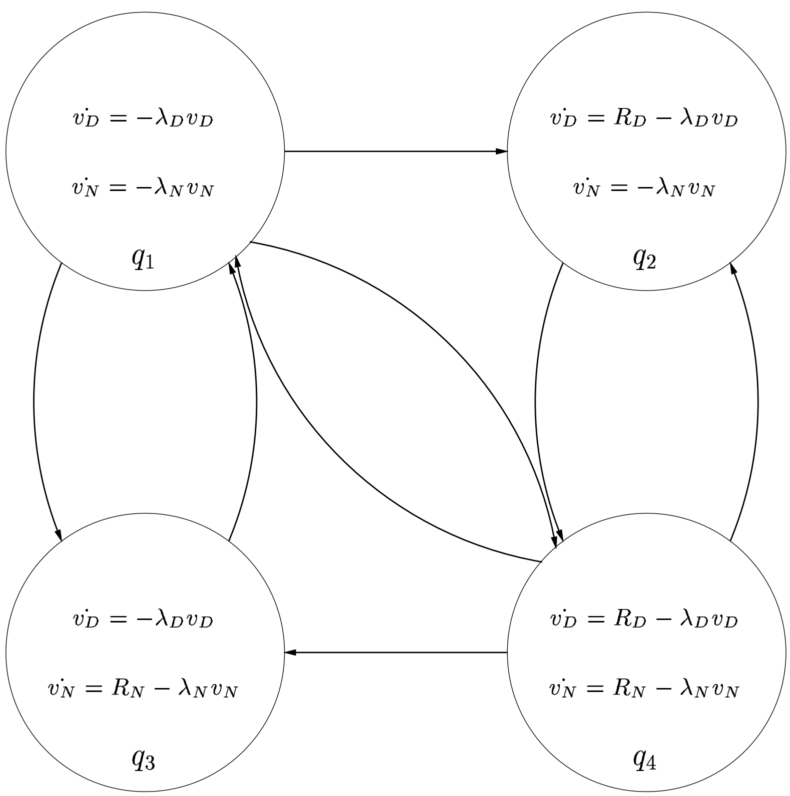

Figure 3: Hybrid system model of individual cell

Hybrid System Model

- N-cell network
  - Compose N hybrid automata
  - Properties of resultant system:
    - $* \; 4^N$ discrete states
    - $* \; 2N$ continuous state variables

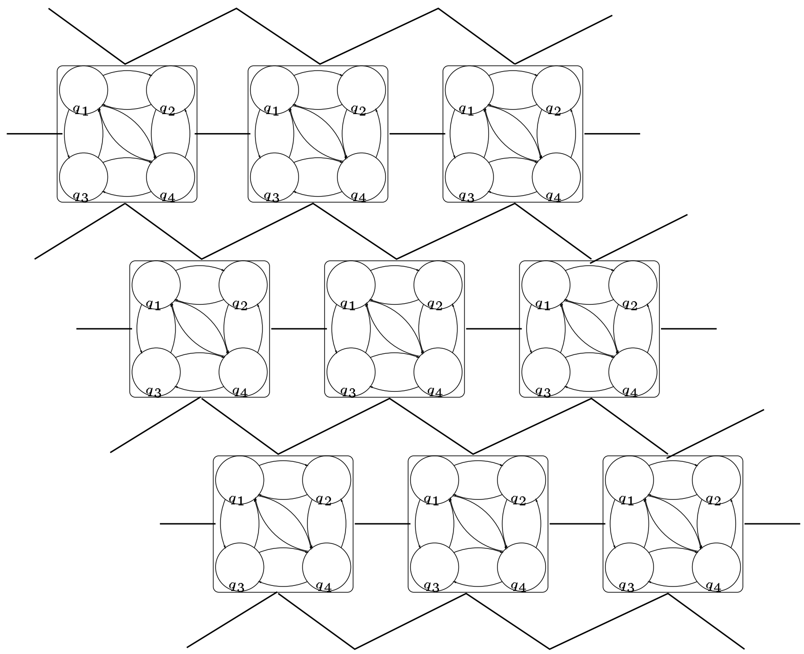

Figure 4: N-cell network

- Simulation
  - Normally distributed initial conditions
  - Uniform boundary conditions assuming undifferentiated cells on perimeter
  - Could also use periodic boundary conditions assuming differentiated cells on perimeter

Simulation Results

- Emergent "salt and pepper" patterns
  - Bistable cell automaton
    - Each cell eventually produces either Notch or Delta, but not both
  - Pattern is sensitive to:
    * Switching thresholds h_D and h_N
    * Initial condition distributions

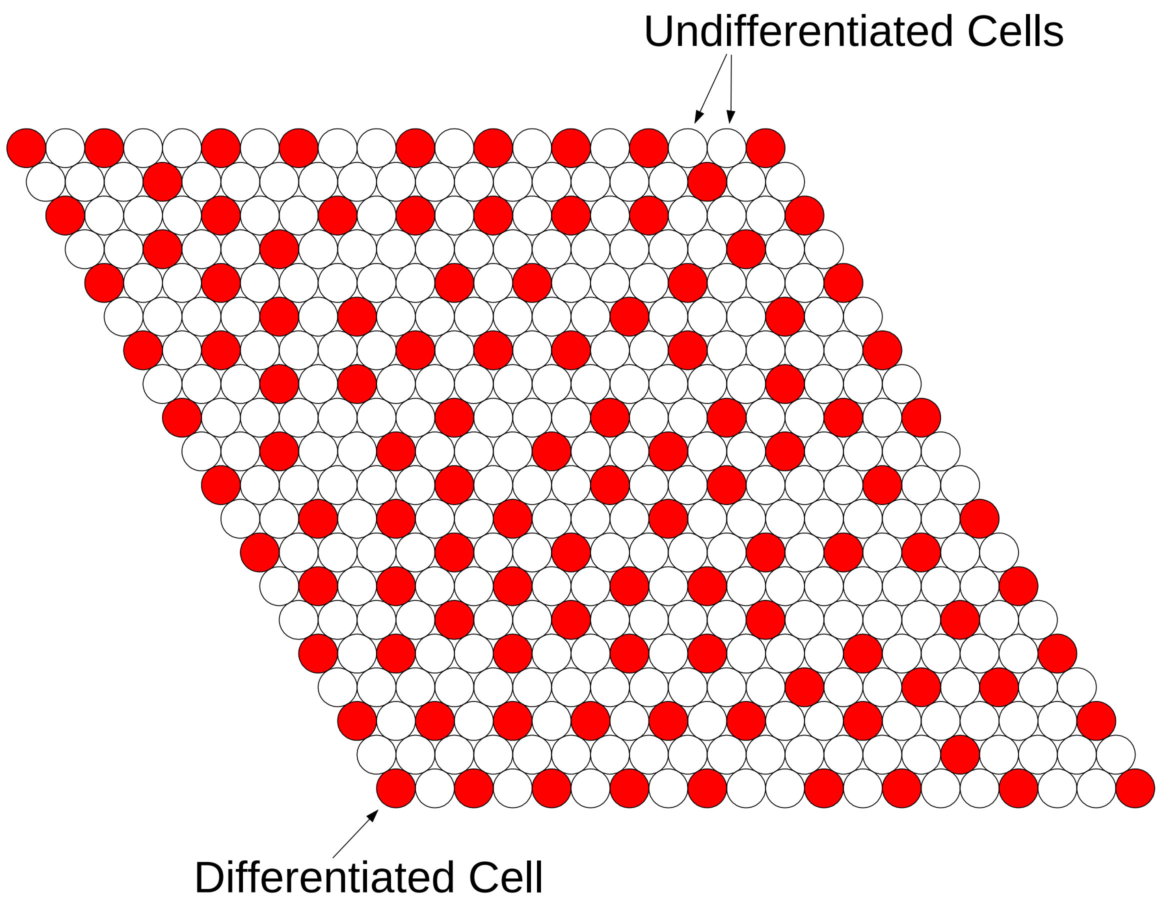

Figure 5: 20×20 cell array showing pattern formation. Red cells are ciliated.

- Interesting result: patterns emerge first at the boundary and then move inwards till steady state

Simulation Results

- Effect of variation in switching thresholds

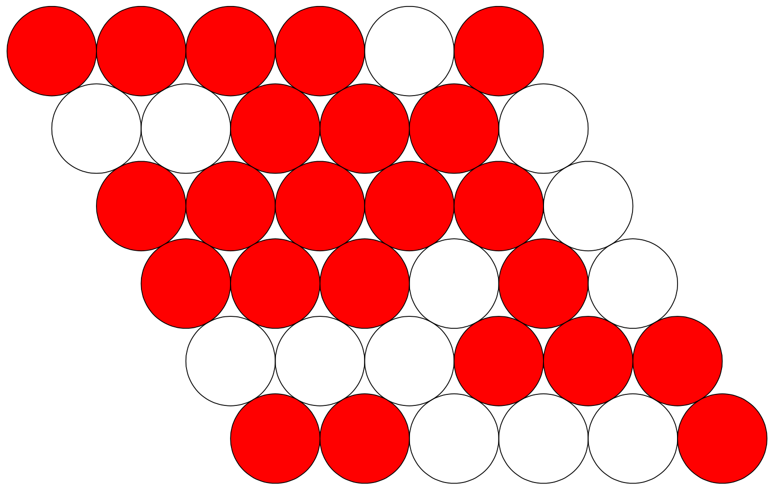

Figure 6: 6×6 cell array with high h_D

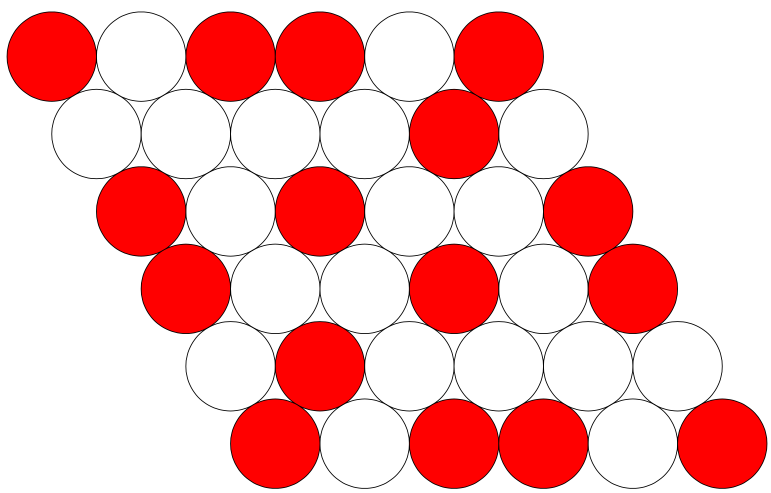

Figure 7: 6×6 cell array with high h_N

- Irregularity: differentiated cells adjacent to each other

Two Cell Hybrid Automaton: Transition Diagram

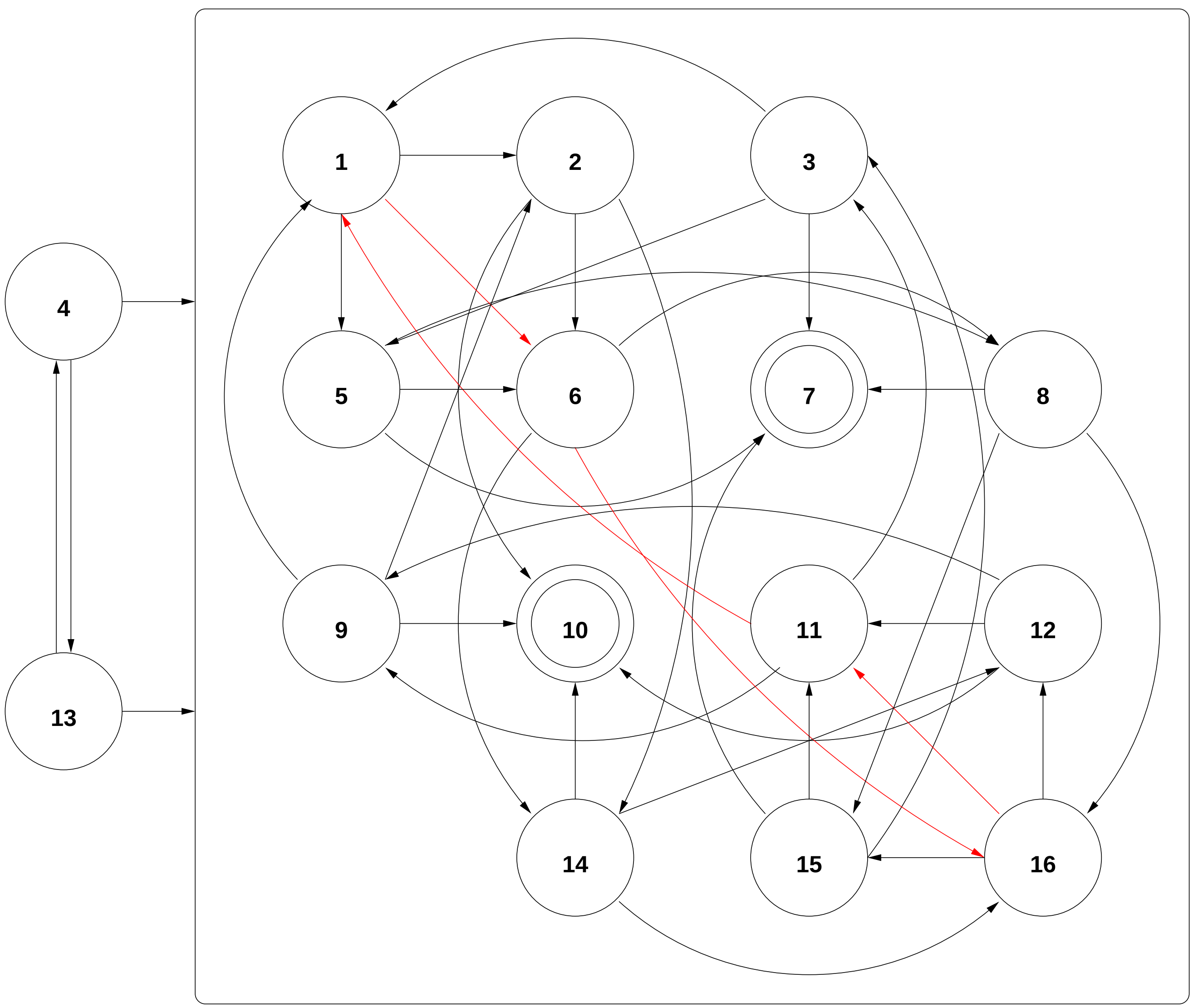

Figure 8: Transition diagram. Note: (1) transitions in red indicate possible cyclic subgraph leading to a Zeno state, (2) numbers 1,. . .,16 in the figure denote modes $q_1, \ldots, q_{16}$ in the hybrid automaton

Research Plan

- Design a "model checker" for biological cell networks
  - the core continuous dynamics are linear (diagonal) systems
  - the discrete dynamics are approximated (bounded) by piecewise linear switches
  - complex feedback loop structure
- Hybrid systems analysis allows:
  - continuous dynamics (majority of computation time) to be "abstracted" in a mathematically correct way
  - a deeper understanding of *cell network behavior*
  - efficient simulation (to predict biological behavior)
  - possible design of control mechanisms